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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,680	10/29/2003	James Frederick Harrington JR.	21486-056	5034

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
02/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/695,680	HARRINGTON, JAMES FREDERICK	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-17,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-17,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 11/27/2007. Claims 1, 21 have been amended and 14, 18 and 19 have been cancelled. Claims 1-13, 15-17, 20, 21 are pending.

Response to Remarks

The rejection of claim 18 under 35 U.S.C 103(a) as being unpatentable over Harrington et al. (Spine. 2000 Apr 15;25(8):929-36) in view of Lawand et al. (Euro J of Pharmacology, 324, (1997), 169-177) as applied to claims 1-7, 12, 13-17,19-20, 21 above and in view of Takahashi et al. (Pain, 75 (1998), 391-394) is withdrawn due to the cancellation of claim 18. Applicants' response regarding the rejection of claims 1-7, 12, 13-17,19-20, 21 under 35 U.S.C. 103(a) as being unpatentable over Harrington et al. (Spine. 2000 Apr 15;25(8):929-36) in view of Slivka (US 2003/0181365, effective filing date Mar 19 2002) and further in view of Lawand et al. (Euro J of Pharmacology, 324, (1997), 169-177) have been fully considered and found not persuasive. Applicants' response regarding the rejection of claims 1, 8,11 under 35 U.S.C. 103(a) as being unpatentable over Harrington et al. (Spine. 2000 Apr 15;25(8):929-36) as applied to claims 1-7, 12, 13-17,19-20, 21 above and in view of Stanfa et al. (Neuroscience, 1999, vol. 93, No. 4, p 1391-1398) have been fully considered and found not persuasive. Applicants' response regarding the rejection of claims 1, 9, 10 under 35 U.S.C. 103(a) as being unpatentable over Harrington et al. (Spine. 2000 Apr 15;25(8):929-36) as applied to claims 1-7, 12, 13-17,19-20, 21 above and in view of Garrett (Biol. Res. for Nursing, Vol. 1, No. 4, Apr 2000) have been fully considered and found not persuasive.

Further search and consideration necessitated the new rejection presented in this office action. Hence the office action is made non-final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 12, 13, 15-17, 20, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington et al. (Spine. 2000 Apr 15;25(8):929-36) in view of Slivka et al. (US 2003/0181365, effective filing date Mar 19 2002) and further in view of Lawand et al. (Euro J of Pharmacology, 324, (1997), 169-177).

Harrington et al. teaches that disc radiculopathy can be treated with epidural glutamate receptor antagonists. The reference teaches that herniated or degenerated disc material contains free glutamate material that acts locally a the dorsal root ganglion to potentiate pain signals (p 935, key points). The reference further teaches that the injections of glutamate receptor antagonists may be beneficial in the radicular pain and other types of spinal pain (p935, lines 13-15). The reference further teaches that administration of intravenous glutamate antagonists can lessen pain responses and intrathecal delivery of glutamate antagonists can attenuate pain behavior (p 934, col. 2, lines 20-26). The reference also teaches that disc radiculopathy may be treated with epidural glutamate receptor antagonists (see Abstract). It is obvious that administration

of glutamate receptor antagonists binds to the glutamate receptors and inhibits the binding of free glutamate.

The reference does not teach a tear in a disc annulus and the administration of glutamate antagonist directly to said herniated disc tissue.

Slivka et al. teach a method of treating pain in a living being such as one caused by a bulging intervertebral disc injecting medication directly into the disc (para 044, example 2, p 7, claim 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer glutamate antagonist directly to said herniated disc tissue. Annulus tears can be a precursor of herniated disc or damage by tear can cause herniated disc. Harrington teaches that glutamate originating from degenerated disc may diffuse to the dorsal root ganglion and effect glutamate receptors and that local injections of glutamate receptor antagonist may be beneficial in the treatment of radicular pain and other types of spinal pain. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to administer glutamate antagonist directly to said herniated disc tissue to relieve radicular pain and spinal pain as taught by Harrington. Also, it is known in the prior art of injecting drugs or medication to the disc directly for the treatment of pain. Slivka et al. teach a method of treating pain in a living being by injection medication into the center of the intervertebral disc. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to administer medication directly to the herniated disc to alleviate pain. One of ordinary skill in the art would have been motivated in administering the glutamate receptor

antagonists directly into herniated disc tissue for the treatment of pain in expectation of success because Harrington teach that local injections of glutamate receptor antagonist may be beneficial in the treatment of radicular pain and other types of spinal pain and Slivka teach a method of administering drugs directly into the disc. to relieve pain caused by bulging intervertebral disc.

The reference does not teach an ionotropic glutamate receptor or NMDA type receptor antagonist in a method to alleviate pain in mammal.

Lawand et al. teaches the intra-articular injection in knee joint of either an NMDA or a non-NMDA glutamate receptor (CNQX) attenuated the thermal hyperalgesia and the mechanical allodynia produced by glutamate, arginine and aspartate (see Abstract). This addresses claims 2-4, 7, 12, 15, 16 and 20. The reference also teaches that the administration of MK-801 reduced the induced thermal hyperalgesic response (p 174, col. 2, lines 26-27) and thus addresses claims 5 and 6. The reference further teaches that attenuation of pain related behavior by intra-articular application of NMDA and non-NMDA excitatory amino acid antagonists after full development of the knee joint inflammation suggests a novel and viable alternative for pharmacological reduction of joint pain associated with inflammation (p 177, col. 2-7).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer ionotropic glutamate receptor or NMDA type receptor antagonist in a method to alleviate pain in mammal. The motivation to do so is taught by Harrington and Lawland et al. Harrington teach the release of free glutamate ions in disc degeneration and further teaches that local injections of glutamate receptor antagonist

may be beneficial in the treatment of radicular pain. Lawland teach that intra-articular injection in knee joint of either an NMDA or a non-NMDA glutamate receptor (CNQX) attenuated the thermal hyperalgesia and the mechanical allodynia produced by glutamate. Hence one of ordinary skill in the art would have been motivated to administer such compounds to alleviate pain by inhibition of binding of free glutamate released (such as lumbar radioculopathy).

The references do not teach a method of alleviating pain in the elbow joint tissue of a mammal comprising administering a glutamate receptor antagonist.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer a glutamate receptor antagonist in a method to alleviate pain in the elbow joint tissue. The motivation to do so is taught by Lawland. The reference teaches that attenuation of pain related behavior by intra-articular application of NMDA and non-NMDA excitatory amino acid antagonists after full development of the knee joint inflammation suggests a novel and viable alternative for pharmacological reduction of joint pain associated with inflammation (p 177, col. 2-7). Elbow joint is another joint like knee joint and hence one of ordinary skill in the art would have been motivated to alleviate the pain in the elbow joint by administration of glutamate receptor antagonists as Lawland teaches the NMDA and non-NMDA antagonists role in attenuation of pain in knee joint inflammation.

Claims 1, 8, 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington et al. (Spine. 2000 Apr 15;25(8):929-36) in view of Slivka et al. (US 2003/0181365, effective filing date Mar 19 2002) and further in view of Lawand et al.

(Euro J of Pharmacology, 324, (1997), 169-177) as applied to claims 1-7, 12, 13, 15-17, 20, 21 above and further in view of Stanfa et al. (Neuroscience, 1999, vol. 93, No. 4, p 1391-1398).

Harrington et al., Slivka et al. and Lawland et al. teachings discussed as above.

The references do not teach a method of alleviating pain by administering KA receptor antagonists and binding of free glutamate to mGlu2 receptor.

Stanfa et al. teaches the administration of non-NMDA receptor antagonists NBQX (AMPA, Glu R1-4 subunit) and LY383884, a KA receptor antagonist directly to the spinal cord of rats (col. 1, p 1392). The reference teaches the enhanced role of AMPA and Kainate antagonists in spinal nociceptive processing in inflammatory states (see Abstract) thus addressing claims 8 and 11.

It would have been obvious to one of ordinary skill in the art to use KA receptor antagonists in a method of treatment to alleviate pain. The motivation to do is provided by Harrington et al. and Stanfa et al. Stanfa et al. teaches the enhanced role of AMPA and Kainate antagonists in spinal nociceptive processing in inflammatory states. Harrington teaches the release of free glutamate ions in disc degeneration and further teaches that local injections of glutamate receptor antagonist may be beneficial in the treatment of radicular pain. Hence one of ordinary skill in the art would have been motivated to administer a KA receptor antagonist compound to alleviate pain by inhibition of binding of free glutamate released in conditions like herniated disc.

Claims 1, 9, 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington et al. (Spine. 2000 Apr 15;25(8):929-36) in view of Slivka et al. (US

2003/0181365, effective filing date Mar 19 2002) and further in view of Lawand et al. (Euro J of Pharmacology, 324, (1997), 169-177) as applied to claims 1-7, 12, 13, 15-17, 20, 21 above and further in view of Garrett (Biol. Res. for Nursing, Vol. 1, No. 4, Apr 2000).

Harrington et al., Slivka et al. and Lawland et al. teachings discussed as above.

The references do not teach a method of alleviating pain by administering metabotropic glutamate receptor antagonists.

Garrett teaches that L-AP3 a metabotropic glutamate receptor antagonist exhibited an antinociceptive effect in animals linking effective treatment of hyperalgesia with metabotropic glutamate receptor (p 316, col. 2, lines 5-9). This addresses claims 9 and 10.

It would have been obvious to one of ordinary skill in the art to use metabotropic glutamate receptor antagonists in a method of treatment to alleviate pain. The motivation to do is provided by Harrington and Garrett. Garett teaches the crucial role of excitatory amino acid, glutamate, NMDA and non-NMDA receptors in pain transmission, pain modulation, central sensitization and the sensation of hyperalgesia (see Abstract, p 311, col. 1, lines 15-44). The reference further teaches that L-AP3 a metabotropic glutamate receptor antagonist exhibited an antinociceptive effect in animals linking effective treatment of hyperalgesia. Harrington teaches the release of free glutamate ions in disc degeneration and further teaches that local injections of glutamate receptor antagonist may be beneficial in the treatment of radicular pain. Hence one of ordinary skill in the art would have been motivated to administer a metabotropic glutamate

receptor antagonist in conditions like degenerated disc to alleviate pain by inhibition of binding of free glutamate released in conditions like herniated disc.

Response to Arguments

Applicants' argue that from the teaching of Harrington et al. one of ordinary skill in the art would not have been motivated to administer the glutamate receptor antagonist into an elbow joint as claimed in claim 17. In response, the claim has been rejected with the combined teachings of Harrington and Lawland. Lawland teach the administration of that intra-articular injection in knee joint of either an NMDA or a non-NMDA glutamate receptor (CNQX) attenuated neuropathic pain and Harrington teach that local injections of glutamate receptor antagonist may be beneficial in the treatment of radicular pain. As explained above, elbow joint is another joint like knee joint and hence one of ordinary skill in the art would have been motivated to alleviate the pain in the elbow joint by administration of glutamate receptor antagonists as Lawland teaches the NMDA and non-NMDA antagonists role in attenuation of pain in knee joint inflammation. Also, the knee and elbow are articulating surfaces or joints and hence it would have been obvious to one of ordinary skill in the art to administer an NMDA and non-NMDA antagonists that has been shown to attenuate pain in knee joint inflammation in alleviating pain in elbow joint.

Applicants' argue that Stanfa et al. does not cure the deficiencies in the teachings of Harrington. In response, Harrington's teachings are directed to the release of free glutamate ions in disc degeneration and the role of glutamate receptor antagonists in alleviating pain and Stanfa et al. teaches the administration of non-NMDA

receptor antagonists NBQX (AMPA, Glu R1-4 subunit) and LY383884, a KA receptor antagonist directly to the spinal cord of rats and the enhanced role of AMPA and Kainate antagonists in spinal nociceptive processing in inflammatory states. As stated earlier it would have been obvious to one of ordinary skill in the art to use KA receptor antagonists in a method of treatment to alleviate pain from the combined teachings of Harrington and Stanfa. One of ordinary skill in the art would have been motivated to administer a KA receptor antagonist compound to alleviate pain by inhibition of binding of free glutamate released in conditions like herniated disc.

Applicants' argue that Garrett does not cure the deficiencies in the teachings of Harrington. In response, Harrington's teachings are directed to the release of free glutamate ions in disc degeneration and the role of glutamate receptor antagonists in alleviating pain and Garrett teaches that L-AP3 a metabotropic glutamate receptor antagonist exhibited an antinociceptive effect in animals linking effective treatment of hyperalgesia with metabotropic glutamate receptor. It would have been obvious to one of ordinary skill in the art to use metabotropic glutamate receptor antagonists in a method of treatment to alleviate pain from the teachings of Harrington and Garrett. Garett teaches the crucial role of excitatory amino acid, glutamate, NMDA and non-NMDA receptors in pain transmission, pain modulation, central sensitization and the sensation of hyperalgesia and further teach that L-AP3 a metabotropic glutamate receptor antagonist exhibited an antinociceptive effect in animals linking effective treatment of hyperalgesia. One having ordinary skill in the art would have been motivated to administer a metabotropic glutamate receptor antagonist in conditions like

degenerated disc to alleviate pain by inhibition of binding of free glutamate released in conditions like herniated disc.

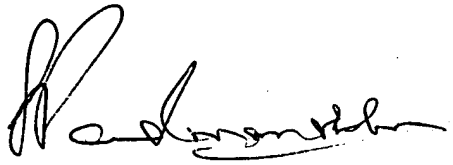
Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



SUPERVISORY PATENT EXAMINER